PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

9/674,492

Applicant's or agent's file reference 1067/2	**FOR FURTHER ACTION**	See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)
International application No. PCT/IL99/00252	International filing date *(day/month/year)* 12 MAY 1999	Priority date *(day/month/year)* 12 MAY 1998
International Patent Classification (IPC) or national classification and IPC IPC(7): G01N 33/00, 33/48 and US Cl.: 436/63, 96; 435/2, 4		
Applicant ADVANCED NEUROPROTECTIVE SYSTEMS LTD.		

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.

2. This REPORT consists of a total of 7 sheets.

   [X] This report is also accompanied by ANNEXES, i.e., sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority. (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

   These annexes consist of a total of 4 sheets.

3. This report contains indications relating to the following items:

   - I [X] Basis of the report
   - II [ ] Priority
   - III [X] Non-establishment of report with regard to novelty, inventive step or industrial applicability
   - IV [ ] Lack of unity of invention
   - V [X] Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
   - VI [ ] Certain documents cited
   - VII [ ] Certain defects in the international application
   - VIII [X] Certain observations on the international application

Date of submission of the demand	Date of completion of this report
29 NOVEMBER 1999	17 MAY 2000
Name and mailing address of the IPEA/US Commissioner of Patents and Trademarks Box PCT Washington, D.C. 20231 Facsimile No. (703) 305-3230	Authorized officer MAUREEN WALLENHORST Telephone No. (703) 308-0661

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International application No.
PCT/IL99/00252

I. Basis of the report

1. With regard to the elements of the international application:*

☐ the international application as originally filed

☒ the description:
pages (See Attached) , as originally filed
pages _____ , filed with the demand
pages _____ , filed with the letter of _____

☒ the claims:
pages (See Attached) , as originally filed
pages _____ , as amended (together with any statement) under Article 19
pages _____ , filed with the demand
pages _____ , filed with the letter of _____

☒ the drawings:
pages (See Attached) , as originally filed
pages _____ , filed with the demand
pages _____ , filed with the letter of _____

☒ the sequence listing part of the description:
pages (See Attached) , as originally filed
pages _____ , filed with the demand
pages _____ , filed with the letter of _____

2. With regard to the **language**, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.
These elements were available or furnished to this Authority in the following language _____ which is:

☐ the language of a translation furnished for the purposes of international search (under Rule 23.1(b)).

☐ the language of publication of the international application (under Rule 48.3(b)).

☐ the language of the translation furnished for the purposes of international preliminary examination (under Rules 55.2 and/or 55.3).

3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international preliminary examination was carried out on the basis of the sequence listing:

☐ contained in the international application in printed form.

☐ filed together with the international application in computer readable form.

☐ furnished subsequently to this Authority in written form.

☐ furnished subsequently to this Authority in computer readable form.

☐ The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.

☐ The statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.

4. ☒ The amendments have resulted in the cancellation of:

☒ the description, pages none

☒ the claims, Nos. none

☒ the drawings, sheets/~~fig~~ none

5. ☒ This report has been drawn as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed, as indicated in the Supplemental Box (Rule 70.2(c)).**

** Replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report since they do not contain amendments (Rules 70.16 and 70.17).*

*** Any replacement sheet containing such amendments must be referred to under item 1 and annexed to this report.*

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III. Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

1. The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non obvious), or to be industrially applicable have not been and will not be examined in respect of:

☐ the entire international application.

☒ claims Nos. 37-39

because:

☐ the said international application, or the said claim Nos. _ relate to the following subject matter which does not require international preliminary examination *(specify)*.

☒ the description, claims or drawings *(indicate particular elements below)* or said claims Nos. 37-39 are so unclear that no meaningful opinion could be formed *(specify)*.

Claims 37-38 will not be examined because they a multiple dependent claim should refer to other claims in the alternative only. Claim 39 will not be examined because a multiple dependent claim cannot depend from any other multiple dependent claim. See PCT Rule 6.4(a).

☐ the claims, or said claims Nos. _ are so inadequately supported by the description that no meaningful opinion could be formed.

☐ no international search report has been established for said claims Nos. _.

2. A meaningful international preliminary examination cannot be carried out due to the failure of the nucleotide and/or amino acid sequence listing to comply with the standard provided for in Annex C of the Administrative Instructions:

☐ the written form has not been furnished or does not comply with the standard.

☐ the computer readable form has not been furnished or does not comply with the standard.

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V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. statement

Novelty (N)	Claims	(Please See supplemental sheet)	YES
	Claims	(Please See supplemental sheet)	NO
Inventive Step (IS)	Claims	(Please See supplemental sheet)	YES
	Claims	(Please See supplemental sheet)	NO
Industrial Applicability (IA)	Claims	(Please See supplemental sheet)	YES
	Claims	(Please See supplemental sheet)	NO

2. citations and explanations (Rule 70.7)

Claims 1-6, 16 and 21-26 lack novelty under PCT Article 33(2) as being anticipated by Munz-Hoyos et al.

Munz-Hoyos et al. teach of a method for diagnosing a predisposition to epilepsy by 1) obtaining a urinary sample from both a patient thought to suffer from epileptic seizures and from a normal, control patient, 2) measuring the amount of kynurenine metabolites in the urinary samples, and 3) comparing the level of kynurenine metabolites between the normal control and epileptic patients. The kynurenine metabolites measured include kynurenic acid, kynurenine, 3-hydroxyantranilic acid and 3-hydroxykynurenine.

Claims 1-6, 16, 21-26 and 51 lack novelty under PCT Article 33(2) as being anticipated by Heyes et al. (CA abstract no. 121:105855).

Heyes et al. teach of a method for diagnosing a predisposition to epilepsy by 1) obtaining a serum sample from both a patient thought to suffer from epileptic seizures and from a neurological normal control patient, 2) measuring the concentration levels of L-kynurenine and quinolinic acid in the serum samples and 3) comparing the level of L-kynurenine and quinolinic acid between the normal control and the epileptic patients.

Heyes et al. also teach that human seizure disorders such as epilepsy are caused by an imbalance in the concentrations of kynurenine metabolites such as quinolinic acid and kynurenic acid. Heyes et al. disclose that an antiepileptic medication can cause the reduction in the serum concentrations of quinolinic acid and kynurenic acid, thereby helping to correct the imbalance. Therefore, Heyes et al. teach of a composition for controlling a seizure disorder such as epilepsy which comprises an antiepileptic drug for correcting an imbalance in kynurenine metabolites in a subject.

Claims 7-12 and 27-31 lack an inventive step under PCT Article 33(3) as being obvious over Munz-Hoyos et al.

(Continued on Supplemental Sheet.)

VIII. Certain observations on the international application

The following observations on the clarity of the claims, description, and drawings or on the question whether the claims are fully supported by the description, are made:

Claims 33, 35, 36 and 44-47 are objected to under PCT Rule 66.2(a)(v) as lacking clarity under PCT Article 6 because the claims are indefinite for the following reason(s): On line 2 of claim 33, the phrases "said at least one neuroprotective metabolite" and "said at least one neurotoxic metabolite" lack antecedent basis. Claims 35 and 36 are indefinite since they depend from claim 34. However, there is no claim 34 since the claims have been misnumbered and claim 34 skipped over. Claim 44 is indefinite since independent claim 41 already recites that the at least two kynurenine metabolites include at least one neuroprotective metabolite and at least one neurotoxic metabolite. Therefore, this limitation in claim 44 is redundant with that which is already recited in claim 41.

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Supplemental Box
(To be used when the space in any of the preceding boxes is not sufficient)

Continuation of: Boxes I - VIII

I. BASIS OF REPORT:

This report has been drawn on the basis of the description,
page(s) 1-34, as originally filed.
page(s) NONE, filed with the demand.
and additional amendments:
NONE

This report has been drawn on the basis of the claims,
page(s) 35-38, as originally filed.
page(s) NONE, as amended under Article 19.
page(s) NONE, filed with the demand.
and additional amendments:
Pages 39-42, filed with the letter of 16 May 2000.

This report has been drawn on the basis of the drawings,
page(s) 1-8, as originally filed.
page(s) NONE, filed with the demand.
and additional amendments:
NONE

This report has been drawn on the basis of the sequence listing part of the description:
page(s) NONE, as originally filed.
pages(s) NONE, filed with the demand.
and additional amendments:
NONE

5. (Some) amendments are considered to go beyond the disclosure as filed:
NONE

V. 1. REASONED STATEMENTS:
The report as to Novelty was positive (YES) with respect to claims 7-15, 17-20, 27-33, 35-36, 40-50.
The report as to Novelty was negative (NO) with respect to claims 1-6, 16, 21-26, 51.
The report as to Inventive Step was positive (YES) with respect to claims 13-15, 17-20, 32-33, 35-36, 40-51.
The report as to Inventive Step was negative (NO) with respect to claims 1-12, 16, 21-31.
The report as to Industrial Applicability was positive (YES) with respect to claims 1-33, 35-36, 40-51.
The report as to Industrial Applicability was negative (NO) with respect to claims none.

V. 2. REASONED STATEMENTS - CITATIONS AND EXPLANATIONS (Continued):

Munz-Hoyos et al. fail to teach of measuring ratios of the concentrations of the kynurenine metabolites. However, it would have been obvious to one of ordinary skill in the art to measure the ratios of different kynurenine metabolites in the method of Munz-Hoyos et al. in order to determine how functionally opposite kynurenine metabolites influence one another to cause the disease known as epilepsy.

Claims 7-12 and 27-31 lack an inventive step under PCT Article 33(3) as being obvious over Heyes et al.

Heyes et al. fail to teach of measuring the ratio of the concentration of L-kynurenine to the concentration of quinolinic acid. However, it would have been obvious to one of ordinary skill in the art to measure the ratio of L-kynurenine to quinolinic acid in the method of Heyes et al. in order to determine how functionally opposite kynurenine metabolites influence one another to cause the disease known as epilepsy.

Claims 13-15, 17-20, 32-33, 35-36, 40 and 50 meet the criteria set out in PCT Article 33(2)-(4), because the prior art does not teach or fairly suggest a method for determining the efficacy of treatment with an antiepileptic drug by measuring the concentration of at least two kynurenine metabolites in a sample from a subject, obtaining a ratio of the metabolites to one another, and comparing the ratio to an expected range of values for individuals with diagnosed epilepsy that is controlled by an antiepileptic drug.
Claims 41-49 meet the criteria set out in PCT Article 33(2)-(4), because the prior art does not teach or fairly suggest a method for quantitatively diagnosing a predisposition to epilepsy in a subject by measuring the concentration of at least two kynurenine

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Supplemental Box
(To be used when the space in any of the preceding boxes is not sufficient)

Continuation of: Boxes I - VIII

metabolites in a sample from a subject to form a pattern and a ratio of the at least two metabolites, and comparing the pattern and ratio to a pattern and ratio of values of the at least two kynurenine metabolites for individuals with non-treated epilepsy.

It is noted that a new Written Opinion will not be sent out since there is no record of any Article 19 amendments having been made in the PCT/IPEA/401 (Demand) form, and no Article 19 amendments have been received prior to this time. Therefore, the amendments received 16 May 2000 will be entered at this time and considered in the preparation of this International Preliminary Examination Report (PCT/IPEA/409).

Claims 1-33, 35-36 and 40-51 meet the criteria set out in PCT Article 33(4), because these claims are directed to a method and a diagnostic system for diagnosing a predisposition to epilepsy.

---------- NEW CITATIONS ----------
NONE

25. The diagnostic system of claim 24, wherein said at least two kynurenine metabolites include at least one neuroprotective metabolite and at least one neurotoxic metabolite.

26. The diagnostic system of claim 25, wherein said at least two kynurenine metabolites include a pair of metabolites selected from the group consisting of KA and 3HOAA, AA and 3HOAA, and KYN and 3HOKYN.

27. The diagnostic system of claim 26, wherein a ratio of said concentrations of said pair of metabolites is measured.

28. The diagnostic system of claim 27, wherein said ratio is selected from the group consisting of KA / 3HOAA, (KA+AA) /3HOAA, KA / QUIN, 3HOAA / 3HOKYN, KA/3HOAAxTRP, and (KA+AA)/3HOAAxTRP.

29. The diagnostic system of claim 28, wherein said measurer includes a HPLC.

30. The diagnostic system of claim 28, wherein said measurer includes a fluorimeter.

31. The diagnostic system of claim 28, wherein said measurer includes an immunochemical assay.

32. A method for determining an efficacy of treatment with an AED (anti-epileptic drug) in a subject, comprising the steps of:

(a) obtaining a sample from the subject;

(b) measuring a concentration of at least two kynurenine metabolites in the sample; and

(c) comparing said concentrations to an expected range of values for individuals with diagnosed epilepsy substantially controlled by treatment with an AED, such that the efficacy of treatment with the AED in the subject is determined.

33. The method of claim 32, wherein step (c) comprises the step of determining a ratio of said at least one neuroprotective metabolite and said at least one neurotoxic metabolite, and the method further comprises the step of

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method further comprises the step of:

(d) comparing said ratio to a previously determined ratio in the subject, such that the efficacy of treatment with the AED in the subject is determined.

35. The method of claim 34, wherein step (c) is performed after treatment with the AED is stopped.

36. The method of claim 34, wherein step (c) is performed while treatment with the AED is ongoing.

37. The method of claims 33-36, further comprising the steps of:

(e) measuring a concentration of the AED in the plasma sample of the subject; and

(f) correlating said concentration of the AED with said ratio to determine the efficacy of treatment with the AED in the subject.

38. The method of claims 33-36, further comprising the steps of:

(e) determining a dose of the AED; and

(f) correlating said dose of the AED with said ratio to determine the efficacy of treatment with the AED in the subject.

39. The method of claim 37 or 38, further comprising the step of:

(g) adjusting a treatment regimen for the AED in the subject according to the ratios of said metabolites.

40. The method of claim 32, wherein step (c) is performed such that the efficacy of treatment with the AED in the subject is quantitatively determined according to the step of quantitatively comparing said concentrations to said expected range of values.

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41. A method for quantitatively diagnosing a predisposition to epilepsy in a subject, the method comprising the steps of:

(a) obtaining a sample from the subject;

(b) measuring a concentration of at least two kynurenine metabolites in the sample, including at least one neurotoxic metabolite and at least one neuroprotective metabolite, to form a pattern and a ratio of said at least two kynurenine metabolites for the subject; and

(c) comparing said pattern and said ratio in the sample to a pattern and a ratio of values of said at least two kynurenine metabolites for individuals with non-treated epilepsy, such that if said ratio and said pattern in the sample is similar to said pattern and said ratio for individuals with non-treated epilepsy, a predisposition to epilepsy is diagnosed in the subject, said predisposition being quantitatively determined according to said ratio.

42. The method of claim 41, wherein the sample is a blood sample.

43. The method of claim 41, wherein said at least two metabolites are selected from the group consisting of TRP (tryptophan), KYN (kynurenine), 3HOKYN (3-hydroxykynurenine), AA (anthranilic acid), 3HOAA (3-hydroxyanthranilic acid), KA (kynurenic acid) and QUIN (quinolinic acid).

44. The method of claim 42, wherein said at least two kynurenine metabolites include at least one neuroprotective metabolite and at least one neurotoxic metabolite.

45. The method of claim 44, wherein said at least two kynurenine metabolites include a pair of metabolites selected from the group consisting of KA and 3HOAA, AA and 3HOAA, and KYN and 3HOKYN.

46. The method of claim 45, wherein a ratio of said concentrations of said pair of metabolites is measured.

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47. The method of claim 46, wherein said ratio is selected from the group consisting of KA / 3HOAA, (KA+AA) /3HOAA, KA / QUIN, 3HOAA / 3HOKYN, KA/3HOAAxTRP, (KA+AA)/3HOAAxTRP and KA/(AA + 3HOAA).

48. The method of claim 43, wherein a concentration of each of substantially all of said kynurenine metabolites is measured.

49. The method of claim 43, wherein said concentration of said at least two metabolites is measured by HPLC.

50. A method for evaluating an efficacy of a new AED (anti-epileptic drug) in a subject, comprising the steps of:

(a) obtaining a first sample from the subject;

(b) measuring a first concentration of at least two kynurenine metabolites in the sample;

(c) administering the new AED to the subject;

(d) obtaining a second sample from the subject;

(e) measuring a second concentration of at least two kynurenine metabolites in the sample; and

(f) comparing said first concentration to said second concentration, such that the efficacy of treatment with the new AED in the subject is determined.

51. A composition for controlling epilepsy in a subject, comprising an AED (anti-epileptic drug) for achieving a balance of kynurenine metabolites in the subject, such that an imbalance is corrected.